Salivary Cortisol Responses to Dexamethasone in Adolescents With Posttraumatic Stress Disorder

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ABSTRACT

Objective: Previous studies of adults with posttraumatic stress disorder (PTSD) have found various abnormalities in the regulation of the hypothalamic-pituitary-adrenal axis, including enhanced suppression of cortisol following low-dose dexamethasone. The purpose of the present study was to investigate salivary cortisol responses to low-dose dexamethasone in adolescents with PTSD. **Method:** Forty-eight adolescents (20 with current PTSD, 9 trauma controls without PTSD, and 19 healthy nontraumatized controls) were enrolled in the study. On day 1, baseline saliva samples were obtained at 8 A.M. and 0.5 mg of dexamethasone was administered at 11 P.M. Cortisol and dexamethasone levels were assessed at 8 A.M. the following day. **Results:** Adolescents with current PTSD showed no difference in the suppression of salivary cortisol in response to low-dose (0.5 mg) dexamethasone compared to trauma controls without PTSD and nontraumatized controls. More severely affected PTSD subjects with co-occurring major depression showed higher pre- and post-dexamethasone salivary cortisol levels compared to controls. **Conclusions:** The present study did not find evidence for enhanced suppression of salivary cortisol at 8 A.M. following low-dose dexamethasone in multiply traumatized adolescents with PTSD. This result differs from findings in adults with PTSD. Further investigations of hypothalamic-pituitary-adrenal axis abnormalities in traumatized children and adolescents are needed. *J. Am. Acad. Child Adolesc. Psychiatry*, 2003, 42(11):1310–1317. **Key Words:** adolescents, posttraumatic stress disorder, low-dose dexamethasone suppression test.

Recent years have witnessed increasing awareness by mental health professionals of high rates of intrafamilial and community-based trauma and posttraumatic stress disorder (PTSD) in adolescents. Community epidemiologic studies of older adolescents estimate rates of PTSD to be 6% (Giaconia et al., 1995). However, in clinical settings, rates of PTSD are higher: 32% in one study conducted on an adolescent inpatient psychiatric unit (Lipschitz et al., 1999) and 22% in one psychiatric outpatient clinic (Silva et al., 2000).

The hypothalamic-pituitary-adrenal (HPA) axis is a critical neurohormonal system involved in the mammalian stress response. Activation of the HPA axis in response to extreme stress leads to the release of many neurohormones, including cortisol, an adrenal steroid that mobilizes energy stores, modulates immune responses, and alters central nervous system information processing in a manner that promotes defensive behavior in the face of perceived threat. The latter effect is mediated by the influence of cortisol on the frontal cortex, amygdala, hippocampus, and locus ceruleus (Lupien et al., 1999; Newcomer et al., 1999; Sapolsky, 1985; Schulkin et al., 1998), brain areas also thought to play important roles in the production of symptoms and functional disabilities associated with chronic PTSD. Consequently, many studies have investigated

Accepted June 3, 2003.

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Supported by a NARSAD Young Investigators Award and a K23 MH 01789 award to Dr. Lipschitz, by the Children's Clinical Research Center grant M01-RR06022, General Clinical Research Centers Program, NIH, by MH 9555 to Dr. Yehuda, and by a NARSAD Young Investigator Award to Dr. Wang. The authors thank the staff of the Yale-New Haven Adolescent Clinic and Yale Psychiatric Hospital as well as Eileen Billingslea, Roberta Halcott, and Robin Jilton for their help with subject recruitment and assessment.

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0890-8567/03/4211–1310©2003 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/01.chi.0000084832.67701.0d

HPA axis regulation and cortisol responses in adults with PTSD and have found a variety of abnormalities.

The most consistent finding to date has been the observation of enhanced suppression of circulating cortisol to a low dose (0.5 mg) of dexamethasone, as reported in two studies of combat veterans with PTSD (Yehuda et al., 1993, 1995) and one study of adult female survivors of childhood sexual abuse (Stein et al., 1997). In contrast, nonsuppression of cortisol to a standard 1-mg dose of dexamethasone has been found in several though not all studies of major depressive disorders (APA Task Force on Laboratory Tests in Psychiatry, 1987; Carroll, 1982), most reliably in psychotic depression (Nelson and Davis, 1997).

To date, few studies have examined HPA axis regulation in traumatized children (DeBellis et al., 1994, 1999; Kaufman et al., 1997b). In 1994, DeBellis and colleagues reported that sexually abused girls had significantly lower basal and exogenous CRF-stimulated plasma ACTH levels but comparable total 24-hour urinary cortisol levels compared to girls who were not sexually abused. In that study, only 2 of the 13 sexually abused girls had PTSD. In a later study, DeBellis and colleagues (1999) found higher urinary cortisol levels in children with PTSD compared to healthy children. Kaufman and colleagues (1997b) also found greater ACTH response to CRF among 13 depressed abused children (8 with PTSD) compared to 13 healthy controls and 13 depressed nonabused children (0 with PTSD). When the depressed abused group was divided into high versus low ACTH responders, there was a trend for a greater number of subjects with PTSD to be among the high responders.

There has been only one prior evaluation of glucocorticoid negative feedback in traumatized adolescents (Goenjian et al., 1996). In that study, a low-dose (0.5 mg) dexamethasone test was performed in 35 teenagers 5 years after exposure to the 1988 Armenian earthquake. Fifteen adolescents who lived close to the earthquake epicenter, and who had more PTSD symptoms, showed lower 4 P.M. cortisol levels in response to administration of dexamethasone at 11 P.M. the night before compared to less-affected adolescents living further from the earthquake epicenter; the 8 A.M. post-dexamethasone results in these two groups were not different. As this study was a field-based, community study of children attending school, structured diagnostic interviews were not conducted. In addition, the study participants were not assessed for medication, alcohol, or nicotine use, all factors known to influence HPA axis function. Further, it was unclear whether adolescents in this study were exposed to other traumatic incidents, either before or after exposure to the earthquake. Additionally, healthy, nontraumatized control adolescents were not included as a comparison group. Thus, the certainty with which these findings can be interpreted is limited.

Therefore, to add to the yet-limited characterization of HPA axis function in adolescents with PTSD, we decided to first determine, in a more completely characterized subject sample, whether adolescents with current PTSD exhibit altered suppression of cortisol after administration of low-dose dexamethasone. Based on previous studies of adults, we hypothesized that adolescents with current PTSD would show enhanced cortisol suppression to dexamethasone compared to traumatized adolescents without PTSD and healthy, nontraumatized adolescents.

METHOD

Participants

Participants were recruited from three sources. All subjects and their parents gave written informed consent to participate in the research protocol, which was approved by the Yale University School of Medicine Human Investigation Committee. Participants were reimbursed financially for their participation.

The first site was an adolescent inpatient unit at Yale Psychiatric Hospital, a private, university-affiliated, urban psychiatric hospital. Over the course of 1 year, 95 admissions were routinely screened for trauma and PTSD; 23% of these teens (n = 24) screened positive for PTSD. Eleven adolescents (10 with PTSD and 1 trauma control) successfully completed the dexamethasone suppression test (DST). The second site was a hospital-based adolescent medical clinic that provides general medical and reproductive health care to an urban inner-city population. One hundred fourteen adolescents were screened for *DSM-IV*-based criterion A trauma and PTSD symptoms (APA, 1994). Fourteen percent of these non-psychiatric treatment-seeking adolescents (n = 12) met the criteria for PTSD. Twenty-eight of these participants (10 with PTSD, 8 trauma controls, and 10 healthy nontrauma controls) completed the low-dose DST. Nine additional, healthy adolescents without *DSM-IV* criterion A trauma, PTSD, or other psychiatric diagnoses were recruited via general advertisements posted in neighborhood supermarkets and community centers. Participants with histories of psychotic disorders, head injury, seizures, or any other neurologic condition were ineligible for the study. All participants were medication-free, except for nine girls on contraceptives. All participants were free of illicit substances as determined by clinical history and urine toxicology screens. Three subjects in the PTSD group smoked.

Diagnostic Assessments

Each participant completed a battery of standardized, self-report questionnaires as part of a screening procedure. These included the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998), a 28-item, self-report inventory that uses a 5-point Likert-

type scale to assess three domains of childhood abuse (sexual, physical, and emotional) and two domains of childhood neglect (physical and emotional); the Child Exposure to Violence Checklist (CEVC) (Amaya-Jackson, unpublished manuscript), a 33-item, self-report checklist that assesses the frequency of exposure to community violence; experiences sampled include being the victim of, witness to, and/or perpetrator of shootings, stabbing, homicide, and family violence; the Child and Adolescent PTSD Checklist (Amaya-Jackson et al., 2000), a 28-item, 4-point Likert-type scale that asks participants to rate the degree to which each of the 17 symptoms of PTSD is present during the past month; and the Beck Depression Inventory (BDI) (Beck and Steer, 1987), a 21-item, self-report inventory that measures cognitive, affective, motivational, and somatic symptoms of depression. (For more details of these measures, see Lipschitz et al., 2000.)

Two master's-level research associates interviewed each participant for the presence and timing of all *DSM-IV* (APA, 1994) criterion A traumas using the PTSD module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997a). Current symptoms of PTSD, occurring within the preceding month, were established with the Child and Adolescent PTSD Checklist (Amaya-Jackson et al., 2000). Next, each adolescent was interviewed with the remainder of the K-SADS-PL to determine additional axis I psychiatric diagnoses. Final psychiatric diagnoses and groupings were determined using a best-estimate approach taking into account results of the self-report questionnaires and the K-SADS-PL. One child psychiatrist (D.S.L.), one adult psychiatrist (A.M.R.), two licensed psychologists (D.C.F. and C.M.G.) and one research associate (E.B.) participated in establishing best-estimate psychiatric diagnoses.

Low-Dose DST

All participants underwent a medical history and physical examination with height, weight, and Tanner staging. Testing took place at the Yale-New Haven Children's Clinical Research Center (CCRC) at Yale-New Haven Hospital. Participants were instructed to wake up at 7 A.M. and not to smoke, eat or drink anything but water, or brush their teeth. At 7:30 A.M. a research assistant met each subject in the lobby of the hospital and escorted him or her to the CCRC. At 8 A.M. saliva samples were collected in Salivette tubes (Sarsedt, Newton, NC). At 10:45 P.M. that evening, subjects were called and reminded to take the 0.5-mg dose of dexamethasone. At 8 A.M. the following day, a research assistant again accompanied the subject to the CCRC, where further samples of saliva were collected. A minimum of 3.5 mL saliva was obtained from each subject for each sample. Salivary samples for cortisol were collected on ice, centrifuged at 1,000*g* for 2 minutes, aliquoted and stored at -70° C for subsequent assay. For the psychiatrically hospitalized participants, saliva samples were collected on the inpatient unit.

Cortisol and Dexamethasone Assays

All assays were conducted blind to diagnostic status. Stored samples were transported on dry ice and analyzed in the laboratory of Rachel Yehuda, Ph.D., at the Bronx VA Medical Center and Mount Sinai School of Medicine. Salivary cortisol levels were assessed with a modified radioimmunoassay kit employing (I^{125}) cortisol (Incstar, Stillwater, MN). A total of 200 µL saliva was incubated with (I^{125}) cortisol and anticortisol serum at room temperature for 2 hours, after which bound and free cortisol were separated. The bound fraction was then counted for 1 minute in a gamma counter. Inter- and intra-assay coefficients of variation were 4.0% and 6.8%, respectively. Salivary dexamethasone levels were measured via radioimmunoassay using a commercially available antibody (IgG Corp., Nashville, TN), as previously described (Yehuda et al., 1993, 1995). Inter- and intra-assay coefficients of variation were 8.0% and 9.0%, respectively.

Statistical Analysis

Subject characteristics of a continuous nature were compared among groups using analysis of variance (ANOVA). χ^2 analyses or Fisher exact tests were used for categorical data. Cortisol data were subjected to a repeated measures analysis of variance with pre- and post-dexamethasone time points as the within-subject measure and diagnostic group as the between-subject factor; dexamethasone levels were used as a covariate. All tests were two-tailed and p values < .05 were considered statistically significant. Data are expressed as means ± standard deviations. Analyses were performed using the Statistical Package for Social Sciences (SPSS-10.0). Post-hoc Bonferroni corrections were used to correct for multiple comparisons.

RESULTS

Clinical Data

Twenty adolescents were assigned a diagnosis of current PTSD. Identified *DSM-IV*-based traumas (APA, 1994) included sexual abuse/assault (n = 11 [55%]), physical abuse/assault (n = 5 [25%]), witnessing community violence (n = 3 [15%]), and witnessing domestic violence (n = 1 [5%]). Coexisting current psychiatric diagnoses in this group included major depressive disorder (n = 14 [70%]), dysthymia (n = 4 [20%]), other anxiety disorders (e.g., social anxiety disorder, simple phobia, and separation anxiety disorder, n = 5 [25%]), and disruptive behavioral disorders (e.g., attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder, n = 8 [40%]). None of these participants met the criteria for a current substance use disorder, although four subjects (20%) met the criteria for a lifetime substance use diagnosis in remission for at least 6 months.

Nine participants endorsed at least one *DSM-IV*-based criterion A1 and A2 trauma but did not meet the criteria for current and/or lifetime PTSD. Identified traumas included sexual abuse/assault (n = 1 [11%]), witnessing community violence (n = 3 [33%]), and vicarious trauma, defined as hearing about the homicide of a first-degree relative or close friend (n = 5 [56%]). Three participants (33%) had a diagnosis of a specific phobia (n = 3 [33%]).

Nineteen participants did not endorse any type of criterion A trauma and did not meet the criteria for any psychiatric diagnoses. They formed the healthy nontraumatized control group. Three subjects in this category had witnessed community violence and/or

reported vicarious trauma but reported no associated responses of fear, horror, or helplessness (criterion A2).

Demographic and physical information about the subjects is summarized in Table 1. Participants ranged in age from 12.3 to 21 years (mean 16.4, SD 2.3 years) and were categorized as Tanner stage IV or V. Twenty-seven percent of participants were white, 60% were African-American, and 13% were Latino. There were no significant differences in height, weight, body mass index, and/or Tanner stage among the three groups of participants. There were no significant differences in age ($F_{2,45}$ = 1.67, p = .20) or gender (Fisher exact test = 3.51, df = 2, p = .17) among groups. There was a trend toward a significant difference in ethnicity (χ^2_4 = 8.53, p = .07) that was accounted for by the high percentage of African-Americans in the trauma control group.

Adolescents with PTSD had experienced a mean of 4.4 ± 1.2 types of trauma compared to trauma controls (mean = 2.4 ± 0.7 types of trauma) (t_{27} = 4.82, p < .001). Compared to trauma controls, adolescents with PTSD had a significantly earlier age of onset (t_{27} = −3.54, p = .001) and a longer duration of trauma exposure (t_{27} = 3.40, p = .002). Data from the CEVC showed that the PTSD and trauma control groups did not differ significantly in rates of witnessed community violence (Fisher exact test = 0.78, df =1, p = .57), nor in rates of vicarious trauma (Fisher exact test = 0.86, df =1, p = .43).

Low-Dose Dexamethasone Challenge

Table 2 shows the mean (± SD) salivary cortisol values at 8 A.M. on the morning before dexamethasone administration (pre-dex cortisol) and at 8 A.M. on the morning after dexamethasone administration (post-dex cortisol), along with the percentage suppression of cortisol and salivary dexamethasone levels.

As indicated by a repeated measures analysis of variance covarying for dexamethasone levels, cortisol decreased in response to low-dose dexamethasone across the three comparison groups (time effect: $F_{1,37}$ = 44.18, p < .001). There were no significant differences among groups in the degree of cortisol suppression by dexamethasone (group by time interaction effect: $F_{2,37}$ = 1.19, p = .32). There was, however, a trend toward a group difference in cortisol levels across all

TABLE 1
Physical, Clinical, and Childhood Trauma Characteristics of Study Participants

	Current PTSD (n = 20)	TC (n = 9)	Healthy NTC (n = 19)	F/χ^2	p
Age (years)	16.4 (2.6)	17.6 (2.5)	15.9 (1.8)	1.66	.20, NS
Gender (M:F)	3:17	1:8	7:12	3.50	.17, NS
Ethnicity, n (%)					
White	7 (35)	1 (11)	5 (26)	8.53	.07, NS
African American	8 (40)	8 (89)	13 (68)		
Latino	5 (25)	—	1 (6)		
Body mass index (kg/m^2)	30.2 (10.5)	27.8 (6.5)	26.1 (6.6)	1.01	.37, NS
Height (cm)	165.4 (10.0)	161.7 (10.1)	167.4 (10.3)	0.89	.42, NS
Weight (kg)	81.7 (27.9)	72.5 (15.0)	72.6 (17.1)	0.91	.41, NS
Smokers	3	—	—	4.48	.11, NS
Oral contraceptive users, n (%)	1 (6)	4 (50)	5 (42)	6.41	.04
Beck Depression Inventory score	13.8 (10.3)	5.1 (5.6)	5.0 (5.9)	6.83	.003
Child and Adolescent PTSD Checklist: no. of PTSD symptoms endorsed					
Cluster B	3.5 (0.9)	2.1 (1.2)	0.5 (0.8)	42.65	<.001
Cluster C	5.1 (1.3)	3.0 (1.9)	0.5 (0.5)	55.29	<.001
Cluster D	3.7 (1.1)	2.2 (1.9)	0.4 (1.1)	28.42	<.001
Childhood Trauma Questionnaire score					
Physical abuse	10.4 (5.7)	5.1 (0.3)	5.3 (0.7)	10.78	<.001
Sexual abuse	11.2 (6.9)	5.0 (0.0)	5.0 (0.0)	9.67	<.001
Emotional abuse	14.7 (5.1)	7.2 (2.7)	6.4 (1.8)	21.52	<.001
Physical neglect	9.7 (4.6)	6.4 (1.9)	6.0 (2.6)	5.63	.005
Emotional neglect	13.1 (5.2)	7.8 (3.7)	6.7 (2.3)	12.91	<.001

Note: Values represent mean (SD) or n (%). TC = trauma controls; NTC = nontraumatized controls; PTSD = posttraumatic stress disorder; NS = not significant.

TABLE 2
Cortisol and Dexamethasone Levels in Adolescent Study Participants

	Current PTSD (n = 20)	Trauma Controls (n = 9)	Healthy NTC (n = 19)	F	p
8 AM pre-dex cortisol (nmol/L)	664 (352)	339 (111)	561 (367)	3.06	.06[a]
8 AM post-dex cortisol (nmol/L)	172 (207)	128 (143)	93 (80)	1.27	.29, NS
8 AM post-dex dexamethasone (ng/mL)	44 (55)	209 (392)	133 (271)	1.38	.26, NS
Percent suppression	73% (27)	65% (33)	79% (25)	0.94	.39, NS

Note: NTC = nontraumatized controls; PTSD = posttraumatic stress disorder; NS = not significant.
[a] Post hoc Bonferroni test shows significant differences between group with current PTSD and trauma controls.

time points ($F_{2,37}$ = 2.91, p = .07) that appeared to be accounted for by the generally higher cortisol levels in the PTSD group.

In secondary analyses, we examined possible influences on cortisol responses to low-dose dexamethasone administration by level of trauma exposure, the use of nicotine and oral contraceptives, ethnicity, and presence of co-occurring depression. When we added the CTQ score as a covariate to the repeated measures analysis of variance, cortisol decreased in response to low-dose dexamethasone administration across the three comparison groups (time effect: $F_{1,41}$ = 5.22, p = .03), but there were no significant differences among groups in the degree of cortisol suppression by dexamethasone (group by time interaction effect: $F_{1,41}$ = 2.34, p = .11).

Removal of the nine girls using contraceptives yielded similar results (group by time interaction effect: $F_{1,21}$ = 2.31, p = .12). Removal of the three smokers with PTSD from the analyses did not result in any significant difference among groups in the degree of cortisol suppression by dexamethasone (group by time interaction effect: $F_{1,34}$ = 0.97, p = .39). Removal of the three subjects in the nontrauma control group who had experienced an adverse event without any accompanying distress did not result in any significant difference among groups in the degree of cortisol suppression by dexamethasone (group by time interaction effect: $F_{1,34}$ = 1.85, p = .18). Using ethnicity as the between-subject factor did not result in any significant difference among groups in the degree of cortisol suppression by dexamethasone (group by time interaction effect: $F_{1,37}$ = 0.42, p = .67). Finally, we examined whether the presence of a co-occurring episode of major depression was associated with the cortisol response to low-dose dexamethasone. A repeated measures analysis of variance using four groups (PTSD and depression [n = 14]; PTSD and no depression [n = 6], trauma controls [n = 9], and healthy controls [n = 19]) revealed that cortisol decreased in response to low-dose dexamethasone across the four comparison groups (time effect: $F_{1,36}$ = 51.35, p < .001) and that there were no significant differences among groups in the degree of cortisol suppression by low-dose dexamethasone administration (group by time interaction effect: $F_{3,36}$ = 0.90, p = .45). There was, however, a significant overall group difference in cortisol levels across time ($F_{3,36}$ = 3.99, p = .01).

Table 3 displays the mean (± SD) salivary cortisol values at 8 A.M. on the morning before (pre-dex cortisol) and on the morning after (post-dex cortisol) dexamethasone administration, along with the percentage suppression of cortisol and salivary dexamethasone levels for the four groups. Post-hoc one-way ANOVAs

TABLE 3
Salivary Cortisol Levels in Adolescents With PTSD/Depr, PTSD Alone, TC, and Healthy NTC

	PTSD Depr (n = 14)	PTSD Alone (n = 6)	TC (n = 9)	Healthy NTC (n = 19)	F
8 AM pre-dex cortisol (nmol/L)	755 (349)	451 (272)	339 (110)	562 (360)	3.47*
8 AM post-dex cortisol (nmol/L)	229 (226)	40 (19)	128 (143)	93 (80)	3.30*
8 AM post-dex dexamethasone (ng/mL)	41 (54)	49 (62)	209 (392)	133 (271)	0.91
Percent suppression	67% (30)	87% (10)	65% (33)	79% (19)	1.59

Note: PTSD/Depr = posttraumatic stress disorder and depression; TC = trauma controls; NTC = nontraumatized controls.
* p < .05.

revealed an effect of group on the 8 A.M. baseline cortisol level ($F_{3,44} = 3.47$, $p = .02$) and the 8 A.M. post-dex cortisol level ($F_{3,44} = 3.30$, $p = .03$). Scheffé contrasts showed that the significant difference in baseline cortisol among the four groups was accounted for by an increase in cortisol in the PTSD/depression group versus the trauma control group ($p = .03$). The significant difference in the post-dex cortisol level appeared to be accounted for by trends for an increase in cortisol in the PTSD/depression versus PTSD alone groups ($p = .08$) and PTSD/depression versus healthy nontraumatized controls ($p = .08$). Self-reported depressive symptoms and posttraumatic symptoms were highly correlated ($r_{47} = 0.53$, $p < .001$), and adolescents in the PTSD/depression group had significantly higher levels of posttraumatic stress symptoms compared to adolescents with PTSD alone (mean PTSD score = 34.1 [SD = 13] versus mean PTSD score = 22.3 [SD = 6.7]; $t_{19} = 1.98$, $p = .053$).

DISCUSSION

The present study did not find evidence for enhanced suppression of 8 A.M. salivary cortisol following low-dose (0.5 mg) dexamethasone in multiply traumatized adolescents with or without PTSD. Adolescents with current PTSD, traumatized adolescents without PTSD, and healthy, nontraumatized adolescents responded similarly to the low-dose dexamethasone test. This finding is in contrast to reports of enhanced suppression of 8 A.M. plasma cortisol to a low dose of dexamethasone in combat veterans with PTSD (Yehuda et al., 1993, 1995) and in adult female survivors of childhood sexual abuse (Stein et al., 1997). However, our findings are similar to those from the study by Goenjiaan and colleagues (1996), the only other study of traumatized adolescents to date. This study reported 88% suppression of cortisol at 8 A.M. in adolescents with greater severity of PTSD symptoms after exposure to a natural disaster (an earthquake) compared to 87% suppression of cortisol at 8 A.M. in adolescents with fewer PTSD symptoms.

There are several possible explanations for the difference in results between this and previous low-dose DST studies in adult subjects with PTSD. First, neurobiologic changes associated with early stress may vary during different developmental periods. For example, there is evidence of differences in HPA axis functioning among children, adolescents, and adults with major depressive disorder. The hypercortisolemia often found in adults with major depression has not been consistently documented in children with major depression (Kaufman et al., 2001). In a review of 29 studies, Dahl and colleagues (1992) noted that only 40% to 60% of adolescents with major depression displayed nonsuppression of cortisol to a 1-mg dose of dexamethasone. This number is lower than rates of nonsuppression in studies of adults with major depression (American Psychiatric Association, 1987; Carroll, 1982).

Differences in subject characteristics and experimental design also may account for differences among DST studies in PTSD. One example is nicotine use. While acute nicotine use increases plasma cortisol levels (Sellini et al., 1989), chronic nicotine use has been associated with both increased plasma cortisol levels (Baron et al., 1995) as well as decreased baseline and stimulated plasma cortisol levels (Krishnan-Sarin et al., 1999). In the current study, removing the three smokers from the PTSD group did not significantly alter our results. Although smoking rates were not reported in previous DST studies in PTSD, they may have been higher in the adult combat veterans and adult women with PTSD than in our adolescents, and this may have influenced study outcomes.

DST studies in PTSD also vary in regard to whether plasma total or salivary free cortisol was measured. While plasma total cortisol and salivary free cortisol are generally correlated (Kirschbaum and Hellhammer, 1994), agents such as oral contraceptives have different effects on these measures (Kirschbaum et al., 1999). Concurrent use of psychotropic medications by some subjects (Stein et al., 1997) or recently discontinued psychotropic medications (Yehuda et al., 1993) also may influence cortisol suppression by dexamethasone via effects on central CRF activity and central glucocorticoid receptors (Barden et al., 1996).

Finally, the activity levels of participants have differed across previous studies of cortisol output and dexamethasone suppression in PTSD and even between diagnostic groups within individual studies, and this may have influenced study outcomes (Rasmusson et al., 2001).

Future DST studies in PTSD should strive to control carefully for all of the aforementioned factors.

In this study adolescents with current PTSD and depression had significantly higher levels of posttraumatic stress symptoms and were functioning more poorly than teens with PTSD alone. This was reflected biologically in that these adolescents had higher baseline and post-dexamethasone salivary cortisol levels but

unaltered reactivity to low-dose dexamethasone. Future studies should examine the relationship between diagnostic comorbidity and neuroendocrine dysfunction in traumatized youngsters. Whether more severe PTSD with depressive symptoms leads to hypercortisolemia or whether hypercortisolemia may contribute to the severity of PTSD and the development of a diagnosable depressive disorder is not clear.

It is also interesting to note the difference in dexamethasone levels among the study groups, with the PTSD group level being lowest. Recent work has demonstrated that prolonged hypercortisolemia decreases the half-life of dexamethasone in plasma, probably by inducing hepatic enzymes that metabolize dexamethasone (Stokes et al., 2002).

Limitations

There are several limitations to the current study. First, we assessed salivary cortisol at only one time point, 8 A.M., on the day following dexamethasone administration. In the only other DST study in traumatized adolescents, Goenjiaan and colleagues (1996) assessed salivary cortisol at two time points, 8 A.M. and 4 P.M. Future studies thus may want to measure cortisol levels at several time points following dexamethasone administration. Lower doses of dexamethasone, such as 0.25 mg, also could be used to detect differences in cortisol response.

In the current study, the majority of adolescents with a diagnosis of current PTSD also met the criteria for major depression. Because of the small number of participants with PTSD alone, our statistical analyses did not allow for an adequately powered comparison between subjects with PTSD alone and those with both PTSD and depression. Future studies thus should be designed with these statistical power issues in mind.

A third limitation is that we did not control for menstrual cycle phase in our female participants. Healthy women exhibit greater suppression of cortisol by dexamethasone in the follicular phase compared to the luteal phase of the menstrual cycle (Altemus et al., 1997). In future neurohormonal studies of postpubertal females with PTSD, subject groups should be matched for menstrual cycle phase.

Finally, the distribution of ethnic groups was not matched across diagnostic groups. Although there was no significant ethnic differences in pre- and post-dexamethasone cortisol levels in the current study, other investigators have noted ethnic differences in HPA axis functioning of African-American and white women (Yanovski et al., 1996). Thus, this variable should be better controlled in future DST studies in PTSD.

Clinical Implications

In recent years, it has become increasingly clear that large numbers of children are exposed to trauma and that some, but not all, develop PTSD. For those who develop PTSD, multiple areas of psychosocial functioning are typically affected during critical periods of development, often leaving the child with enduring deficits. To date, very little has been learned about the underlying pathophysiology of this debilitating disorder. This study has attempted to elucidate one aspect of HPA axis functioning that has been identified as abnormal in adults with PTSD. Although we did not find evidence for enhanced suppression of salivary cortisol by dexamethasone in this group of traumatized adolescents with PTSD, it is possible that a more extensive investigation of HPA axis functioning (e.g., a CRF challenge test, an ACTH challenge test, 24-hour urine and plasma cortisol sampling) would have uncovered abnormalities of cortisol responsivity. Larger, carefully controlled studies that include an evaluation of the diagnostic comorbidity of traumatized children as well as more extensive neurohormonal assessments are needed before we can feel confident regarding the pattern of HPA axis regulation associated with PTSD in youths. This may help us develop a clearer understanding of the similarities and differences between adult and child trauma survivors with PTSD and develop better preventive and treatment-oriented interventions.

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